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Exposures and urinary biomonitoring of aliphatic isocyanates in construction metal structure coating

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ABSTRACT

Background: Isocyanates are highly reactive chemicals used widely in metal structure coating applications in construction. Isocyanates are potent respiratory and skin sensitizers and a leading cause of occupational asthma. At present, there is no cure for isocyanate asthma and no biomarkers of early disease. Exposure reduction is considered the most effective preventive strategy. To date, limited data are available on isocyanate exposures and work practices in construction trades using isocyanates, including metal structure coatings.

Objectives: The primary objectives of this work were: i) to characterize isocyanate inhalation and dermal exposures among painters during metal structure coating tasks in construction; and ii) to assess the adequacy of existing work practices and exposure controls via urinary biomonitoring pre- and post-shift.

Methods: Exposures to aliphatic isocyanates based on 1,6-hexamethylene diisocyanate (1,6-HDI) and its higher oligomers (biuret, isocyanurate and uretdione) were measured among 30 workers performing painting of bridges and other metal structures in several construction sites in the Northeastern USA. Exposure assessment included simultaneous measurement of personal inhalation exposures (n = 20), dermal exposures (n = 22) and body burden via urinary biomonitoring pre- and post-shift (n = 53). Contextual information was collected about tasks, processes, materials, work practices, personal protective equipment (PPEs) and exposure controls, work histories, and environmental conditions.

Results: Breathing zone concentrations were the highest for biuret (median, 18.4 μg/m^3), followed by 1,6-HDI monomer (median, 3.5 μg/m^3), isocyanurate (median, 3.4 μg/m^3) and uretdione (median, 1.7 μg/m^3). The highest exposures, measured during painting inside an enclosed bridge on a hot summer day, were: 10,288 μg/m^3 uretdione; 8,240 μg/m^3 biuret; and 947 μg/m^3 1,6-HDI. Twenty percent of samples were above the NIOSH ceiling exposure limit for 1,6- HDI (140 μg/m^3) and 35% of samples were above the UK-HSE ceiling for total isocyanate group (70 μg NCO/m^3). Isocyanate loading on the gloves was generally high, with a median of 129 μg biuret/pair and maximum of 60.8 mg biuret/pair. The most frequently used PPEs in the workplace were half-face organic vapor cartridge (OVC) respirators, disposable palmar dip-coated polymer gloves, and cotton coveralls. However, 32% of workers didn't wear any respirator, 47% wore standard clothing with short-sleeve shirts and 14% didn't wear any gloves while performing tasks involving isocyanates. Based on biomonitoring results, 58.4% of urine samples exceeded the biological monitoring guidance value (BMGV) of 1 μmol hexamethylene diamine (HDA)/mol creatinine. Post-shift geometric mean HDA normalized to specific gravity increased by 2.5-fold compared to pre-shift (GM, 4.7 vs. 1.9 ng/mL; p value, < 0.001), and only 1.4-fold when normalized to creatinine.

Conclusions: Exposure and biomonitoring results, coupled with field observations, support the overall conclusions that (i) substantial inhalation and dermal exposures to aliphatic isocyanates occur during industrial coating applications in construction trades; that (ii) the current work practices and exposure controls are not adequately protective. High urinary creatinine values in the majority of workers, coupled with significant cross-shift increases and filed observations, point to the need for further investigations on possible combined effects of heat

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stress, dehydration, and nutritional deficiencies on kidney toxicity. Implementation of comprehensive exposure control programs and increased awareness are warranted in order to reduce isocyanate exposures and associated health risks among this cohort of construction workers.

1. Introduction

Reactive chemical resin systems based on isocyanates are used widely in diverse construction applications for their excellent performance characteristics, such as durability, resistance to chemical and physical agents, and optical transparency. Typical applications involving isocyanates include industrial metal structures coatings (bridges, exterior and interior surfaces of industrial storage tanks, water pipes, wind turbines), interior floor coatings, grouts and terrazzo applications, gluing, sealing, concrete bonding, and masonry work. The demand for these products continues to grow, in response to a strong growth in residential construction and the need for repairs in the aging infrastructure. More than 56,000 bridges in the United States are in need of repair or replacement, increasing the expected demand for industrial coating jobs (ARTBA, 2019; Kirk and Mallett, 2018). The number of construction painters accounted for ~380,000 in 2016, and is projected to grow by 6% (or 22,000 new jobs) in the next decade (BLS, 2018). Furthermore, as energy production shifts to renewable sources, the demand for building and maintaining wind turbines will continue to increase, and with it, the demand for industrial coatings. The general industrial coatings market is expected to reach $131 billion by 2022 (Pianoforte, 2019).

Painters exposed to isocyanates are at risk of developing occupational asthma and other isocyanate-related diseases. Isocyanates are potent respiratory sensitizers and have one of the lowest occupational exposure limits ever established (5 parts per billion, ppb time 8-hr time weighted average). Isocyanates continue to be a major occupational health problem (Reilly et al., 2019; Thore and Tiotiu, 2019) and a leading cause of occupational asthma (Goossens et al., 2002; Lefkowitz et al., 2015; Lockey et al., 2015; Redlich et al., 2007), in spite of the fact that their occupational toxicology and health have been studied continuously for more than half a century. In addition to asthma, exposures to isocyanates may also induce hypersensitivity pneumonitis, chronic obstructive pulmonary disease (COPD) and accelerated loss of pulmonary function, allergic and irritant contact dermatitis, rhinitis, irritation of the upper airways, eyes, and skin and occasional skin burns (Geier et al., 2018; Goossens et al., 2002; Wisnewski et al., 2006). Deaths from acute isocyanate expsoures have been reported, although fortunately they tend to be rare (NIOSH, 2006; Reilly et al., 2019; Thore and Tiotiu, 2019).

Occupational asthma continues to be the primary health concern of isocyanate exposures, in part because there is no cure for the disease; sensitized individuals may respond to extremely low isocyanate levels (as low as 1 ppb) at work or do-it-yourslelf consumer applications or cross-react to other isocyanates and amine components in the two-pack formulations; and their asthma may progress towards a generalized, non-specific asthma that may be triggered by other respiratory irritants and pollutants (Lockey et al., 2015; Redlich et al., 2007). At present there are no reliable biochemical tests for detecting isocyanate sensitization, especially in early stages, and clinical diagnosis of isocyanate asthma is complex, invasive and expensive. The current recommendation for the management of isocyanate asthma is complete avoidance or elimination of isocyanate exposures (Baur et al., 2012). However, this solution may come at the cost of significant loss of income for affected workers, while for many of them the isocyanate asthma symptoms do not improve significantly (Ruegger et al., 2014). Therefore, exposure reduction through effective exposure controls is an important intervention strategy, and one that could yield a better long-term outcome in reducing the risk of occupational asthma and preserving the income of these workers (Baur et al., 2012; Vandenplas et al., 2011).

Little is known about exposures and disease prevalence among construction trades that use isocyanates, in particular industrial coatings. Numerous studies have investigated isocyanate exposures and respiratory disorders (Pronk et al. 2007, 2009) during coating and painting tasks in the automotive and aerospace industries, and other manufacturing sectors that produce polyurethane products (England et al., 2001; Janko et al., 1992; Pronk et al., 2006; Reeb-Whitaker et al., 2012; Reilly et al., 2019; Sparer et al., 2004). Because construction differs in significant ways from aerospace and auto manufacturing industries, the knowledge base about exposures, chemistries, workflow and work practices from those sectors cannot be transferred readily to construction applications. This significant data gap on isocyanate exposures and effectiveness of exposure controls among construction workers must be addressed with relevant field exposure assessment and biomonitoring studies.

The polyurethane coating systems used in construction are often polymeric aliphatic isocyanates based on the 1,6- hexamethylene diisocyanate (1,6-HDI) monomer and/or isophorone diisocyanate (IPDI) referred to as pHDI and pIPDI, respectively (Supplemental Material (SI), Fig. S1). These formulations are often applied as two-part systems, comprised of the isocyanate hardener (part A) and the base part (part B), which is often a mixture of solvent blends, polyols, cross-linkers, and other additives. Current part A formulations contain only traces of the volatile monomer (HDI or IPDI, each typically at < 0.1–1% in commercial formulations), with > 99% of the isocyanate being higher oligomeric species (Bello et al., 2002b; Fent et al., 2009; Sparer et al., 2004). After the hardener is mixed with the base, the product is typically sprayed using a spray gun, or is manually applied using a roller or a brush. Painters are exposed to isocyanates through inhalation of their vapors (for volatile monomers) and airborne aerosols, as well as through direct dermal contact with the product or contaminated tools and surfaces. Comprehensive assessments of inhalation and dermal exposures, supplemented with exposure biomarkers are essential for identifying exposure sources, as well as for evaluating the efficacy of work practices and personal protective equipment (PPE) on reducing exposures. Urinary biomonitoring of isocyanate exposures in a number of studies has relied on measuring the corresponding diamines of monomers, such as HDI and IPDI (1,6-hexamethylene diamine, HDA) and isophorone diamine, IPDA) (Gaines et al. 2010a, 2011; Pronk et al., 2006) following aggressive acid hydrolysis. Because of its short clearance half-life of a few hours (Budnik et al., 2011; Liu et al., 2004) HDA monitoring can be valuable when evaluating the efficacy of exposure controls and PPE within a short time frame such as during a working shift.

We are presenting herein the results of a field investigation that was conducted as part of a larger study on reactive isocyanate systems among construction workers. The objectives of this work were (i) to characterize chemistries of and isocyanate exposures among painters during metal structure coating tasks in construction using simultaneous measurement of air and dermal exposures, and (ii) assess adequacy of existing work practices and exposure controls through field observations and through urinary biomonitoring pre- and post-shift. Results of this work can guide development of future intervention strategies for reducing isocyanate exposure among construction painters.

2. Methods

2.1. Sampling sites and participants

Workplace sampling was performed during topcoat applications at eight unique construction sites in the Northeast United States from May 2015 to October 2018. Thirty participants were recruited over ten field

trips: 23 painters involved directly with product application through spraying, rolling or brushing, 5 helpers who performed product mixing and other auxiliary tasks, and two bystanders (managers). The majority of study participants were males (7% females). Among all participants, 80% were self-identified as White, 7% as Black or African American and 13% mixed race. All participants signed an informed consent form approved by the Institutional Review Board of UMass Lowell.

For presentation purposes, study sites can be classified into three main groups: bridges, indoor spray booth, and 'other sites' (Fig. 1): *Bridges:* Sampling was performed at 4 different bridges during the application of the polyurethane topcoat, which involved spray painting in conjunction with rolling and brushing of difficult to reach surfaces, edges, and tight angles. The number of workers at each site ranged from 3 to 7. In two bridges, painting and other tasks were done inside a tarp enclosure intended to protect fresh paint from dust, and when necessary, to maintain temperature and reduce relative humidity within technical specifications. During hot summer days, temperatures inside these tarp enclosures would exceed 35 °C, and in one occasion, we registered indoor temperatures of 47 °C for several hours. Blow fans were sometimes seen being used inside enclosures. Painting was done during the day shift, with the exception of one enclosed bridge that was painted during the night shift (8PM- 4AM).

Indoor painting shop: Metal bridge components were sometimes painted indoors and transported to the bridge site for assembly, especially during cold weather. Sampling indoor was conducted during two different sampling trips, while the painters applied a polyurethane topcoat on decorative railing and small bridge parts. Painting was performed on the shop floor of a large room (20 × 15 × 6 m). Outdoor air was introduced into the room via a large fan located near the entrance. The two workers at this site painted the small parts using an airless spray gun.

The *'other sites'* consisted of diverse settings and activities, including painting of a large outdoor wind turbine, an elevated water tank (of historical significance), and one experimental nuclear reactor dome attached to a university building. Painting at the reactor dome and water tank was done exclusively with rollers and brushes to avoid dispersion of overspray aerosols to nearby parking lot and building occupants. The number of workers at each site varied from 2 (water tank) to 5 (reactor dome).

The total number of sampling trips and site characteristics are summarized in Table 1. Activities at each site followed a similar pattern, with the main daily activities being site preparation, product mixing, coating application, and some cleanup at the end of the shift. At each site, we conducted workplace observations to capture relevant contextual exposure information on site characteristics, frequency and duration of tasks/activities, number of workers performing each task, type of products in use and manufacturer, product application methods, workers' demographics, types of exposure controls (personal protective equipment, ventilation, enclosures) and environmental conditions, such as temperature and relative humidity.

2.2. Exposure monitoring

Workplace exposure assessment consisted of simultaneous personal airborne and dermal exposure sampling, with concomitant pre- and post-shift urinary biomonitoring.

2.2.1. Personal breathing zone (PBZ) sampling

Personal breathing zone sampling was conducted on 20 workers who consented to wear the sampler for the duration of tasks involving isocyanates (painting, rolling, brushing, mixing, or a combination thereof). Sampling was conducted with a CIP-10MI sampler (Arelco, Fontenay-Sous-Bios Cedex, France) that has been successfully used and validated in spray polyurethane foam applications (Bello et al., 2019). The CIP-10MI sampler collects aerosols inside a sampling cup that rotates at ~6700 rpm inducing an air flow of 10 L/min. The sampling cup

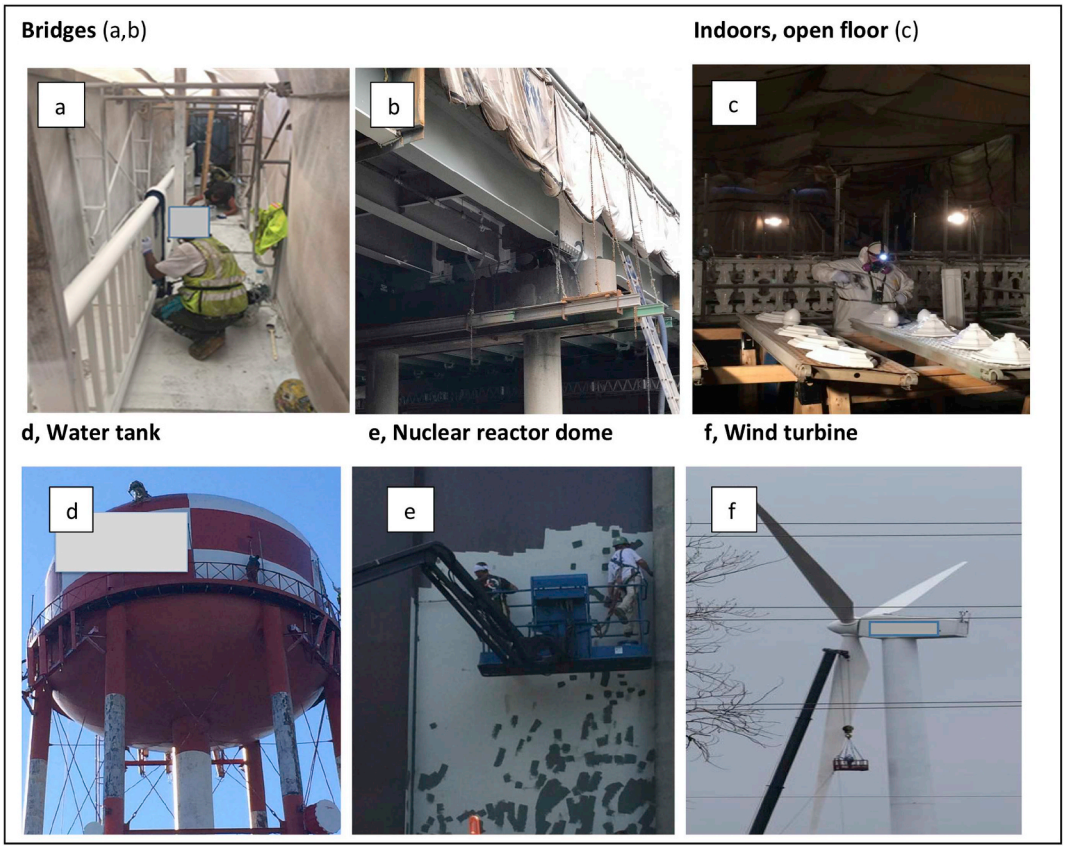


Fig. 1. Representative photographs of typical sampling sites investigated in this project.

Table 1
Summary description of coating sites, sampling trips, and number of air, gloves and urine samples collected.

Sites	Number of sampling sites (no. visits)[a]	Activity	Tasks performed	Environment	Total number of samples		
					Personal breathing zone	Glove pairs	Urine[b]
Bridge painting	4	Polyurethane top coat painting of metal structures in bridges	Roller, brush and spray painting	Tarp enclosure (2) and open air (2) Median temp 80 °F Median RH 69%	11	11	31
Indoor shop	1 (2)	Polyurethane top coat painting of bridge parts inside a painting shop	Spray painting of small parts	Indoors (room size ~20 × 15 × 5 m) Median temp 64 °F Median RH 60%	3	3	8
Wind turbine	1	Polyurethane top coat painting of an installed wind turbine	Spray painting	Tarp enclosure Median outdoor temp 75 °F Median RH 50%	3	1	0
Elevated water tank	1	Polyurethane top coat painting of an elevated water tank	Roller painting	Open air painting Outdoor temp, 50 °F RH 63%	2	2	4
Reactor Dome	1 (2)	Polyurethane mid- and top coat painting of an experimental nuclear reactor dome	Roller and brush painting	Open air painting Median outdoor temp 88 °F RH 47%	1	5	10
Total	8 (10)				20	22	53

[a] In a few occasions, some sites were visited a second time on a different day, as in the case of indoor shop painting and the reactor dome (two visits). During these visits, workers would perform similar tasks, but use different materials for different coating layers (e.g. primer or top coat).
[b] Pre- and post-shift urine samples (the only non-paired urine sample was collected post-shift from one bystander at one bridge site).

was filled with 2 mL of 1 mM MAP in butyl benzoate. At the end of the sampling period, the liquid media from the CIP-10MI cup was transferred into clean amber glass vials using disposable lab grade polypropylene pipettes and stored and transported to the lab in coolers with ice packs. In the lab, samples were stored at −20 °C until they were ready for processing and analysis (see chemical analysis section). The overall personal sampling duration had a median of 105 min (range 30–390 min). In addition to PBZ samples, we collected six stationary area samples inside the mixing trucks (n = 2), at the mixing stations (n = 2), and in the far field of the sprayer in the indoor painting shop (n = 2).

2.2.2. Dermal exposure sampling

Potential dermal exposures were measured for both hands using a recently validated interception method which consists of a pair of thin medical grade cotton gloves impregnated with the derivatizing MAP reagent, worn over thin nitrile gloves, as previously described by our group (Bello et al., 2019; Harari et al., 2016). Duration of glove sampling had a median of 117 min (range of 30–330 min) depending on workers' preference for wearing the glove dosimeter. For the remainder of their workday, workers continued using their regular selection of gloves, as summarized in the later sections. At the end of sampling, both glove dosimeters were transferred into a 100 mL capacity glass jar containing 50 mL of 50 mM MAP in ethyl acetate (a nontoxic solvent substitute for methylene chloride or acetonitrile) and shaken to ensure gloves were soaked in the solvent. The jars, capped with a PTFE lid, were stored and transported to the lab in coolers with ice packs. When in the lab, another 50 mL ethyl acetate was added to the jar to improve extraction efficiency and jars were stored at −20 °C until ready for chemical analysis.

Of all study participants, 22 consented to wearing the glove dosimeter.

2.2.3. Urine sample collection

Spot urine samples were collected in sterile urine specimen collection cups at the beginning and at the end of the work shift, with exact times depending on work schedules and worker availability. The time interval between pre- and post-shift urine collection had a median of 345 (range 185–525) minutes. From 53 urine samples, 26 were collected pre-shift and 27 post-shift. At the end of sampling, urine samples were transferred immediately inside coolers with dry ice and were transported to the lab, where they were stored at −80 °C until further processing.

Overall, among the 30 study participants, 20 participated in personal air sampling; 22 wore the glove dosimeters; 26 provided pre-shift urine samples; and 27 provided post-shift urine (26 matched pre- and post-shift pairs). The two bystanders (managers) provided only urine samples. A total of 16 workers provided matched air, glove, and pre- and post-shift urine samples.

2.3. Chemical analysis

2.3.1. Sample preparation

Raw bulk isocyanate products from work sites were processed following earlier published protocols (Bello et al., 2002b; Sparer et al., 2004). Briefly, ~0.5 g bulk was diluted 1000 times with methylene chloride in two steps, and 25 µL of this solution was transferred to 975 µL of 0.5 mM MAP in acetonitrile for derivatization. Five µL of acetic anhydride was added to the solution 24 h later. The final solution of the derivatized bulk contained about 30–35 µg/mL isocyanate product. The same derivatization protocol was repeated with Desmodur N100, using deuterated MAP (d_8-MAP), yielding internally labeled isocyanate-MAP derivatives. Internal standards of HDI-d8-MAP, IPDI-d8-MAP, MDI-d8-MAP, were prepared and characterized by Dr. Streicher (NIOSH, Chemical Exposure and Monitoring Branch) as described in our earlier work (Bello et al., 2019; Mellette et al., 2019). Of note, several isocyanate bulks of pHDI, pIPDI, pMDI, and pTDI have been extensively characterized in earlier work (Bello et al. 2002a, 2002b).

Air samples were allowed to warm to room temperature, vortexed for 1 min, diluted 100-1000 × in acetonitrile, spiked with 10 µL of the corresponding internal standard (IS) cocktail (d_8-MAP derivatives of HDI and IPDI at a final concentration of 100 ng/mL each, as well as 10µL of d8-MAP-N100 bulk product, accounting for the additional d8-MAP-HDI), filtered through a 0.45 µm Acrodisc® filter, and analyzed by LC-ESI-MS/MS in the positive electrospray ionization mode (Mellette et al., 2018), as described in detail in a later section and under method validation. For validation purposes, raw bulk isocyanate samples and select air samples were also analyzed with the NIOSH 5525 method (Bello et al., 2002b; NIOSH, 2003).

Glove samples were processed following our earlier published

protocols (Bello et al., 2019; Harari et al., 2016) and analyzed by LC-ESI-MS/MS as described in the subsequent section. Briefly, jars containing gloves were shaken for 5 min to homogenize the sample and then sonicated for 30 min in a water bath. Then a sample aliquot was taken from the jar, diluted 100-1000 × in acetonitrile, spiked with the internal standard (IS) cocktail HDI-d8-MAP and IPDI-d8-MAP and N100-d8-MAP) as done with the air samples, and filtered through two consecutive 0.25 μm filters into a 2 mL amber LC vial to remove cotton fibers and other particulate matter, and were analyzed with LC-ESI-MS/MS (described in later sections).

Urine samples were allowed to thaw in a temperature-controlled water bath at 37 °C. The urine was centrifuged at 1000 rpm for 10 min to remove any cellular debris. At that time, urine specific gravity was measured with a handheld digital pocket refractometer (PAL -10S Atago, Japan). For HDA and IPDA measurements, urine was treated as described in (Bello et al., 2019). Briefly, 1 mL of urine spiked with 100 ng 1,7-heptanediamine (IS) was hydrolyzed with 1.5 mL of 3 M sulfuric acid. After boiling at 100 °C for 12 h, the sample was cooled down to room temperature. The sample was then neutralized with saturated sodium hydroxide NaOH (5 mL) and extracted twice with 3 mL of 0.1% benzoic anhydride in toluene. Benzoic anhydride was added to improve the absolute extraction efficiency of HDA and IPDA (results section). Two 3 mL extracts were added together, the solvent was evaporated to almost dryness under nitrogen, transferred to a vacuum oven at room temperature to dry completely, and reconstituted with 250 μL of methanol. The final sample was analyzed by LC-ESI-MS/MS, by monitoring the MRM transitions of the derivative of benzoic acid derivative of HDA (N,N′-1,6-Hexane-1,6-diylbis (benzamide)), as described later, IPDA and the corresponding IS with 1,7-heptanediamine. Quality control measures included running urine blanks, spikes, blind samples, replicates, conducting recovery studies, and a secondary blind analysis of a subset of 15 samples.

2.3.2. LC-ESI-MS/MS analysis of air and dermal isocyanate samples

Air, dermal and bulk samples were analyzed for isocyanates with a highly sensitive and selective LC-ESI-MS/MS method with an online UV diode array detector (DAD). The system was an API 3200 (Applied Biosystems, Foster City, CA) and a complete Shimadzu 20AD stack (two pumps, refrigerated autosampler, degasser, column compartment, and DAD). The analytical method quantifies HDI, its dimer uretdione, trimers biuret and isocyanurate, IPDI-1 and IPDI-2, and IPDI trimer (isocyanurate) and di-isocyanurate. The detection and quantification of analytes were performed in the MRM (multiple reaction monitoring) mode. (SI Fig. S2). MS source parameters for the API3200 were: curtain gas (CUR) 15, collision gas (CAD) 5, ion spray voltage 5500, source temperature 650 °C, ion source gas 1 and 2 (GS 1, GS2) 60 and 50, respectively, and interface heater was ON. Optimized MRM compound parameters for all analytes and IS are presented in SI, Table S1.

Separation was accomplished using a Kinetex C18 column (4.6 × 100 mm, 2.6 μm particle size) (Phenomenex, Torrance, CA) using mobile phase A, 0.1% (w/v) ammonium acetate in water, and mobile phase B, 0.1% (v/v) formic acid in acetonitrile. The column oven temperature was set to 40 °C and sample injection volume to 10 μl. The flow rate was 0.6 mL/min with a linear gradient from 60% to 95% B over 10 min, followed by an isocratic 95% B until 15 min, and 3 min column re-equilibration. Quantitation of HDI and IPDI were accomplished with individual calibration curves using high purity HDI-MAP and IPDI-MAP and their respective IS (HDI-d8-MAP and IPDI-d8-MAP). These purified standards were obtained from Dr. Streicher at NIOSH and purity verified with HPLC (> 99% pure). The calibration curves were linear with an R^2 of. 0.999 for HDI and 0.998 for IPDI. The linear range of HDI and IPDI standard curves was from 0.25 ng/mL to 1000 ng/mL. Samples that exceeded the upper linear range in MS were diluted (typically 10-100 ×) and rerun again. The LOD of HDI and IPDI were 0.05 ng/mL and 0.03 ng/mL, respectively, based on a signal-to-noise (S/N) ratio > 3 of the lowest quantifiable standard. Limit of quantitation (LOQ) of HDI and IPDI were 0.15 ng/mL and 0.1 ng/mL, respectively (determined as a S/N ratio of 10).

There are no analytical standards commercially available for higher oligomers of HDI uretdione, HDI biuret, and HDI isocyanurate (either as purified isocyanate species or as MAP derivatives) or pIPDI. MAP-isocyanate species have a nearly identical response factor in UV (Bello

Table 2
Component analysis of aliphatic isocyanate bulk samples and reference Desmodur N100 by NIOSH 5525/ISO Method 17735 (HPLC/FLD/DAD) and LC-ESI-MS/MS. The current LC-ESI-MS/MS yields equivalent amounts of major isocyanate species content in bulks to the validated NIOSH 5525 method (regression coefficient LC-ESI-MS/MS (y) = 1.021 × NIOSH 5525; R^2 = 0.994; *t*-test for difference, p = 0.33).

Product[a]	METHOD	% by mass in product					Other species[c] (molar %)	% NCO (w/w)
		HDI	HDI uretdi-one	HDI biuret	HDI isocyanur-ate	pIPDI[b]		
Desmodur N100 (Reference)	LC-ESI-MS/MS	2.95	6.49	68.7	8.82	–	–	16.1
	NIOSH 5525	2.91	6.32	68.2	9.5	–	13.0	16.5
Acrolon 218 (Bridge site)	LC-ESI-MS/MS	3.04	12.12	77.33	7.51	–	–	25.2
	NIOSH 5525	3.85	11.42	76.75	8.14	–	–	25.4
Acrolon 281 (Indoor site)	LC-ESI-MS/MS	3.01	11.96	77.87	7.16	–	–	25.3
	NIOSH 5525	3.07	11.52	76.15	6.92	–	–	25.3
Corothane (reactor dome coating; mix of pMDI, pHDI, pIPDI, pTDI)[d]	LC-ESI-MS/MS	2.68	19.2	0.10	34.8	15.3	–	18.0
	NIOSH 5525	2.74	18.92	0.11	25.6	15.8	27.8	24.9
High solids polyurethane, (indoor site, bridge parts painting)	LC-ESI-MS/MS	1.33	10.59	60.32	4.08	–	–	21.3
	NIOSH 5525	1.29	14.33	58.96	4.33	–	22.1	30.4
Bona Traffic HD™ (Floor coating; pHDI +pIPDI)	LC-ESI-MS/MS	0.53	0.20	0.20	69.91	–	–	17.9
	NIOSH 5525	0.43	0.18	0.17	68.79	–	29.2	25.7

[a] Acrolon 218 was the main product used in metal structure coatings. Corothane was used as an intermediate coat at only one site; Bona Traffic HD™ was encountered in floor coating applications, not metal structure coatings.

[b] pIPDI based on the online UV 254 nm detector; includes multiple species. pIPDI, isocyanurate = 5.3%; pIPDI diisocyanurate = 10%, as measured by the online UV detection in LC-ESI-MS/MS.

[c] Other species, not quantified in MS/MS because it requires further method development. Explains the difference in tNCO between the two methods. The reported percentage is a molar ratio, not a mass ratio, and provides an estimate of the relative abundance of these unknown species relative to known species. Includes unknown isocyanates species (reaction byproducts during application), different isocyanates, or other species that have identical absorption properties with isocyanates (UV254 absorption and FL Ex = 370, Em = 418).

[d] Safety data sheet (SDS) lists pMDI, pTDI and ~1% of p-benzensulfonic isocyanate (pBSI). LC-ESI-MS/MS confirmed presence of pMDI, pHDI, and pIPDI. We did not test for pTDI and para-benzenesulfonic isocyanate (pBSI), which is rather unstable.

et al., 2002b; NIOSH, 2003), allowing quantitation of each compound based on calibration curves of the respective monomer. Because the response factor in MRM is highly structure dependent, we developed individual MS adjustment factors for these analytes based on the online UV responses, described in detail in the SI section. This approach has been used successfully for pMDI species (Bello et al., 2019; Mellette et al., 2019). The MRM adjustment factors relative to HDI MRM response factor were as follows: uretdione, 0.64 × (relative standard deviation RSD, 4.2%), biuret, 8.42 × (0.6%), isocyanurate, 7.11 × (8%) (SI, Table S2). These factors were used to divide the amount of these analytes as predicted from the HDI MRM calibration curve.

2.3.3. Validation of the LC-ESI-MS/MS against ISO17735/NIOSH 5525 method

This quantitative LC-ESI-MS/MS method was then validated against the NIOSH method 5525 for isocyanates (NIOSH, 2003) which is also an ISO method (ISO 17735: 2019). The NIOSH 5525 method relies on MAP-derivatization but employs different separation (pH gradient, buffers) and detection systems (DAD and FLD detectors). This method has been evaluated and applied extensively in multiple large-scale studies by our group and NIOSH researchers. One significant advantage of this approach is its versatility (can be applied to many other similar isocyanate products) and cost-effectiveness. We diluted several bulk samples from the work sites as well as Desmodur N100 (comparative material) and analyzed them according to the NIOSH 5525 method on an Agilent 1100 HPLC equipped with a DAD and a Fluorescence (FLD) system (Bello et al. 2002a, 2002b, 2008) and by LC-ESI-MS/MS. The agreement between the two methods (NIOSH 5525 and LC-ESI-MS/MS with adjustment response factors) was excellent (Table 2), both yielding nearly identical concentrations of major analytes in HDI based polyisocyanates. Furthermore, the total NCO derived from LC-ESI-MS/MS was nearly identical to NIOSH 5525 for Acrolon and Desmodur N100 (comparative material), which are topcoat materials encountered in bridges. The LC-ESI-MS/MS method does underestimate the calculated TNCO for some products that contain additional species not measured in MS/MS.

2.3.4. LC-ESI-MS/MS analysis of urinary biomarkers

HDA (biomarker of HDI) and IPDA (biomarker of IPDI) were converted to the corresponding amides of benzoic anhydride during extraction with toluene. Separation was accomplished using a Kinetex C18 column (4.6 × 100 mm, 2.6 μm particle size) (Phenomenex, Torrance, CA) under gradient elution, with mobile phase A, 0.1% (v/v) formic acid in deionized water, and mobile phase B, 0.1% (v/v) formic acid in methanol. The gradient was as follows: isocratic at 40% B for the first 3 min, then linear gradient to 85% B from 3 to 15 min, hold at 85% for 2 min, followed by 3 min column re-equilibration at 40% B. The ion source of the mass spectrometer was set as follows: curtain gas (CUR) 30, collision gas (CAD) 5, ion spray voltage 5500, source temperature 650 °C, ion source gas 1 and 2 (GS 1, GS2) 55 and 50, respectively, and the interface heater was ON. The MRM compound optimization parameters are presented in SI, Table S1.

For the analysis of biomarkers of HDI and IPDI in urine, we used multiple reaction monitoring (MRM). The standard curve was linear in the range of 0.1 ng/mL to 500 ng/mL, R^2 = 0.9993, and the detection limit of the derivative of benzoic anhydride was 0.1 ng/mL. For quality control, several urine samples (n = 19) were divided into four aliquots of 1 mL each, and spiked with either 0 (control), 1 ng, 10 ng, or 100 ng HDA and 100 ng of 1,7-heptadiamine IS. Then the samples were processed and analyzed as described earlier. The results of the HDA recovery experiments are shown in SI, Table S3. Simultaneous derivatization with 0.1% benzoic anhydride and extraction in toluene resulted in much higher absolute recoveries for HDA (92.2–101.3%) relative to the conventional approach of urinary extraction followed by derivatization (range, 6.09–16.06%), as well as in improved chromatographic retention of HDA-BA and IPDA-BA derivatives and fragmentation patterns in mass spec, resulting overall in a more sensitive method. The much better recovery in our work can be attributed to the fact that HDA has a substantial water solubility (log Ko/w = 0.386), hence it is not extracted efficiently with toluene, whereas its amide derivative with benzoic anhydride is notably more lipophilic. Although the use of IS corrects for lower recoveries, the ~6-16 × lower absolute extraction yield for HDA will likely result in much higher rates of non-detectable HDA in urine samples with the conventional method. Therefore, this urine sample preparation modification may be important.

2.3.5. Creatinine analysis

The concentration of creatinine in each urine sample was quantified using LC-ESI-MS/MS-based on the method of (Hou et al., 2012), as reported in (Bello et al., 2019). The urine was diluted 2000 times in DI water and then 10 μL of d3-creatinine (IS) were added (final concentration, 25 ng/mL). Separation was carried out on a Kinetex C18 column (4.6 × 100 mm, 2.6 μm particle size) (Phenomenex, Torrance, CA) at a flow rate of 600 μL/min, with the column temperature set at 40 °C. Isocratic separation was accomplished with 50% solvent A (0.1% formic acid in water) and 50% solvent B (0.1% formic acid in methanol). The calibration curve was linear from 0.5 ng/mL to 2 μg/mL, R^2 = 1.0. The detection limit of the analytical method for creatinine was 250 pg/mL.

2.4. Statistical analysis

Statistical analyses were performed using the SAS software (9.4 SAS Institute Inc. Cary, NC). Airborne concentrations of all isocyanate species, their mass on gloves, and urinary HDA data were examined for the underlying distribution using the Shapiro-Wilks statistic and by graphing probability plots and histograms. Log-transformed data were used for the statistical analysis.

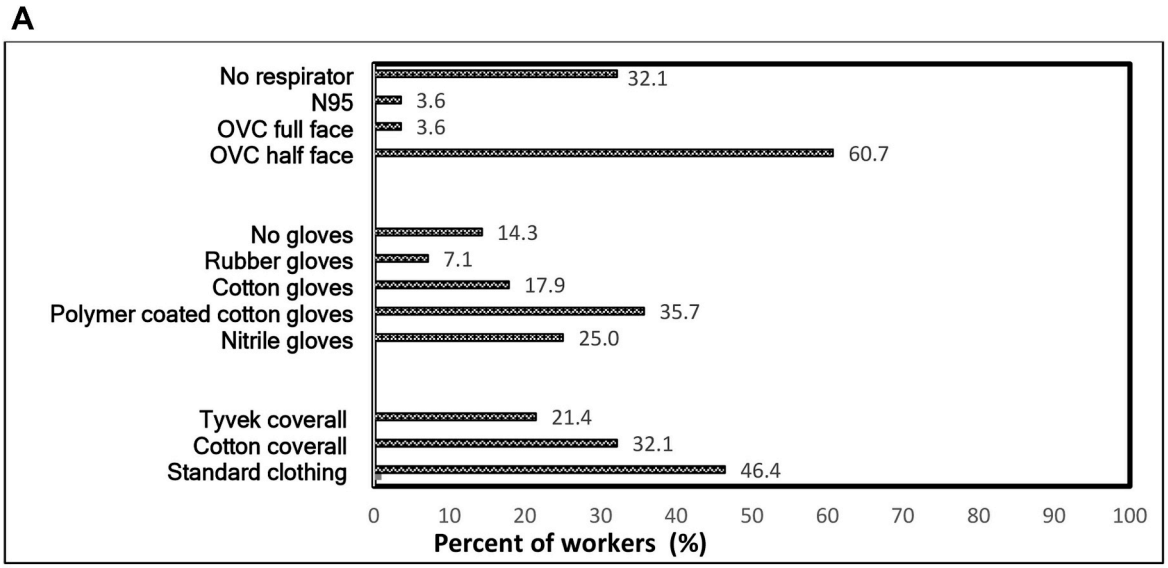
Non-detectable levels were assigned a value equal to method limit of quantitation (LOQ) of the sampling-analytical train divided by two (Hornung and Reed, 1990).

Concentrations of airborne isocyanate species such as 1,6-HDI monomer were compared with NIOSH 10 min ceiling limit of 140 μg/m^3. The estimated total isocyanate group (TNCO) was compared with the Health and Safety Executive (UK HSE) ceiling limit of 70 μg TNCO/m^3 (Bello et al., 2004). Moreover, personal exposures were compared with the NIOSH REL 10-hr TWA and UK HSE 8hr-TWA in two ways: 1) by direct comparison with measured concentrations, assuming the same concentration for the rest of the unsampled time; and 2) by comparison with the calculated daily TWA concentrations assuming zero exposures for the unsampled time.

Linear mixed effects models were utilized to investigate association of airborne exposures with the task performed (spraying, rolling, helping), enclosure (yes, no, indoor), using site ID as a random effect. Linear regression models were used to investigate the impact of ambient temperature and humidity on airborne exposures. Dermal exposures were similarly compared by task performed using site ID as a random effect. Isocyanate loading on gloves, measured as μg isocyanate/pair, was standardized to a one-minute task duration to account for different sampling times across samples. Rolling and brushing tasks were categorized in one category as “rolling”, since in most cases workers used interchangeably both brushes and rollers during painting. In situations where workers performed both spraying and rolling, the task was classified as “spraying”. All tasks associated with product mixing and other supporting activities were defined as " helping”. Exposures between different sites were also compared to identify sites with the highest exposures.

Concentration of HDA in urine was normalized to both creatinine and specific gravity (SG) to adjust for different hydration rates of individual workers. Paired t-tests on log-transformed data were used to examine cross-shift differences on urinary HDA normalized to

creatinine (μmol HDA/mol creatinine) and specific gravity (μg HDA/mL). Univariate and multivariate linear regression models were run to investigate the effect of inhalation and dermal exposures on the post-shift urinary HDA levels (dependent variable). Two different types of models were run: (i) models with HDA normalized to creatinine or specific gravity; and (ii) models with creatinine or specific gravity as separate independent variables (Barr et al., 2005; Gaines et al., 2010b). Different sub models with several combinations of these variables were also investigated. We further explored the influence of PPE used (coveralls, respirators, gloves) and task performed on post-shift urinary HDA levels using linear mixed effects models with site as a random effect.



Legend: Standard clothing involves common cotton or synthetic fabrics. Nitrile gloves were thin, 3 mil gloves. Polymer coated cotton gloves include gloves commonly found at contractor distributors' stores (such as Home Depot) and include polymer coating on the palmar side of the glove.

Fig. 2. a. **Personal protective equipment observed in use at sampling sites (n workers = 30, n sites = 10).** Observations report on the use of PPE during active tasks involving handling, preparation, and application of isocyanate formulations – spraying, roller/brush, mixing, cleanup.

3. Results

3.1. Work practices and personal protective equipment (PPE)

Field observation data summarized in Fig. 2 indicate that the type and frequency of PPE used in workplaces visited varied widely between and within each site. The majority of participants (~61%) used half-face organic vapor cartridge (OVC) respirators, without particulate filter. One worker (3.6%) wore a full-face OVC respirator, another one wore an N95 (3.6%), while 32% of participants did not use any respirator. About 36% of workers wore disposable polymer dip coated gloves (coating on the palmar side only), 25% wore thin nitrile gloves, 18% wore thick cotton gloves, 7% rubber gloves, while 14% of participants didn't use any gloves. Painters used mostly cotton (32%) or polyethylene (22%) coveralls, although standard clothing with short sleeve shirts was also common (46% of participants).

3.2. Raw isocyanate products

The majority of the sites we visited used the same topcoat product, Acrolon 218 (Sherwin Williams Corp.). In Massachusetts, only a limited number of protective coating systems are approved for use in highway bridges steel structures by the Northeast Protective Coating Committee (NEPCOAT). Analysis of isocyanate raw materials acquired at construction sites involved in this study revealed that they were aliphatic pHDI. Aliphatic pHDI is comprised of multiple oligomeric species, the most important being, HDI (monomer), uretdione (a dimer, also referred to as uretidinedione or dione), HDI biuret (trimer), HDI isocyanurate (trimer), as well as multiple other condensation products of biuret and isocyanurate (such as di-biuret, di-isocyanurate, etc.). Biuret was the most abundant compound in the bulk product (~77%), followed by uretdione (~12%) and isocyanurate (3%) (Table 2) with multiple other pHDI species comprising only a minor fraction. However, some products, most notably the Corothane and the high solids floor coating product were notably more complex. The pIPDI was encountered only in the intermediate coat at one site (Corothane), but not top coating of metal structures (Table 2). Quantitation of all these species, some known and others unknown, and the total isocyanate group can be done in HPLC when MAP is used as the derivatizing reagent (Bello et al., 2002b; NIOSH, 2003). The ratios of these main compounds also vary by product blend and manufacturer (Sparer et al., 2004).

3.3. Airborne PBZ exposures

Airborne PBZ isocyanate concentrations varied widely across different sites. Overall, biuret was the predominant analyte in airborne samples. Biuret concentrations (μg/m^3) had a median of 18.4 and range of < 0.1–8,240. Isocyanurate had a median concentration (μg/m^3) of 3.4 and range of < 0.1–182.3. Uretdione in air had a median (μg/m^3) of 1.7 and range of < 0.1–10,288. Concentrations of 1,6-HDI monomer (μg/m^3) had a median of 3.5 and range of 0.02–946.7 (Table 3). Air concentrations of 1,6-HDI were highly correlated with the three oligomers (r = 0.82–0.95) (SI, Table S4). The highest airborne PBZ exposures were measured on a sprayer painting inside an enclosed bridge during a hot summer day, when indoor temperature soared to 46 °C (117 °F). This sample had the highest measured concentrations of uretdione (10,288 μg/m^3), biuret (8,240 μg/m^3), isocyanurate (182 μg/m^3), and 1,6- HDI monomer (947 μg/m^3). The TNCO, calculated as the sum of quantified species (all in μg NCO/m^3), had a median of 4.3, a mean of 415 and range of 0.1–4896.

We found significantly higher exposures during painting inside enclosed spaces and indoors compared to outdoor painting ($p < 0.001$) (Fig. 3). The variable 'enclosure' remained significant for the most volatile 1,6-HDI monomer, even when the temperature was included in the multivariate model ($p < 0.01$). Although spraying was associated with higher potential for airborne exposures compared to rolling tasks (Fig. 4), these results were not statistically significant, most likely due to the small sample size and high exposure variability. There results suggest that substantial exposure to aerosolized paint can also happen during rolling and brushing tasks.

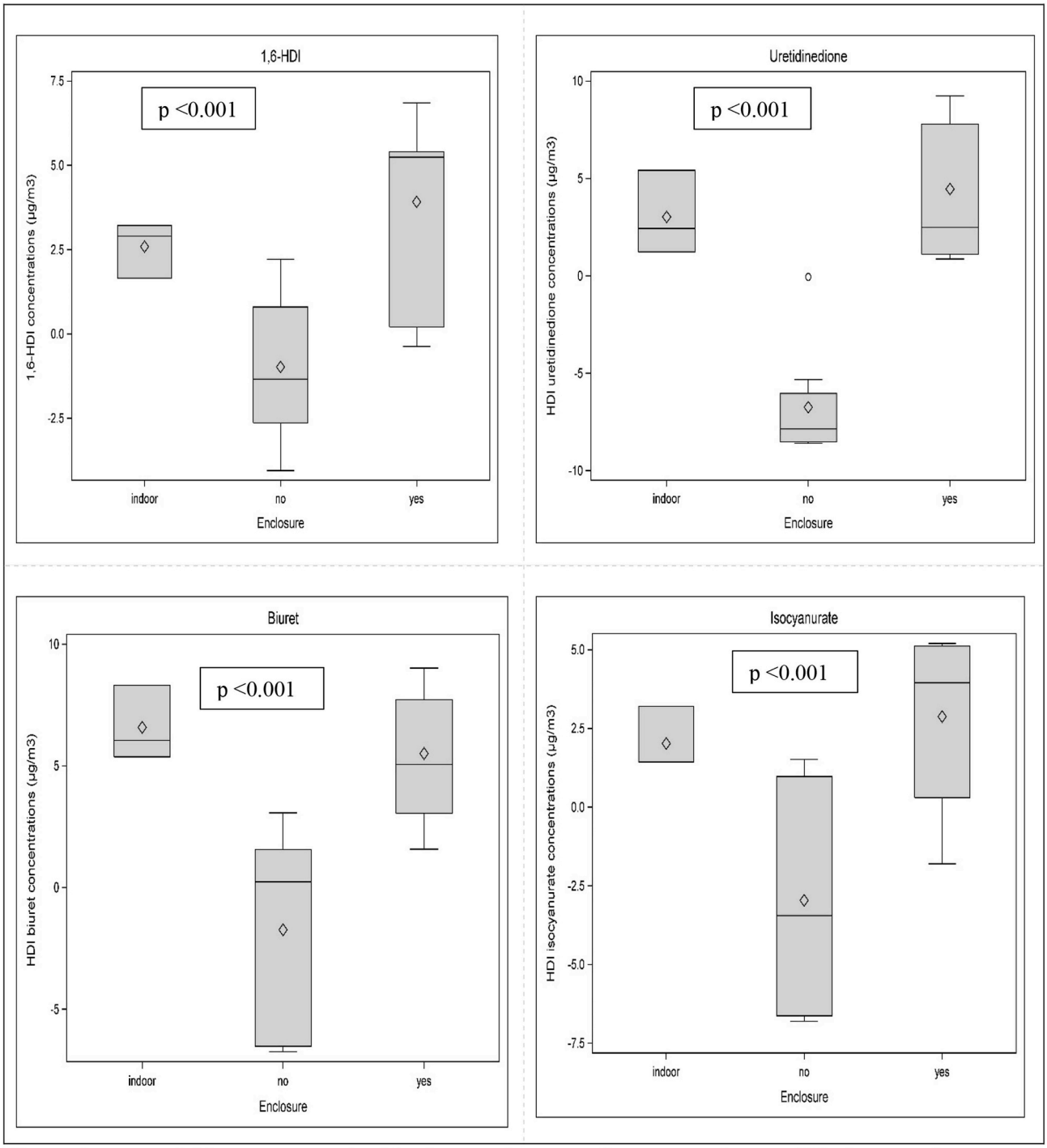
Average outdoor ambient temperature at all sampling sites ranged from 4.4 to 31 °C (median 22 °C), whereas relative humidity ranged from 47 to 99% (median 66%). Humidity was significantly associated with airborne 1,6-HDI and TNCO (p values < 0.001) exposures, but the temperature was not ($p = 0.5$ &0.9, respectively).

Far field area samples at the indoor site indicate high exposures inside the spraying room at levels that were comparable with personal breathing zone samples (Table S5). The highest levels were measured for biuret at 787.6 μg/m^3 on one sample located at the entrance of the spray room. All other stationary area samples collected inside the trucks and near mixing stations at other sites had non-detectable or very low exposures to isocyanate species measured samples.

Table 3
Personal breathing zone (PBZ) and potential dermal exposures to aliphatic isocyanate measured among workers performing metal structure coating in construction.

Isocyanate Species [a]	Inhalation exposures [b] (n = 20)				Dermal exposures [c] (n = 22)						
	Non-detects (%)	*Breathing zone concentrations (μg/m^3)*			Non-detects (%)	*Glove loading (μg isocyanate/pair)*			*Glove loading (μg isocyanate/pair/min)*		
		Mean	Median	Range		Mean	Median	Range	Mean	Median	Range
HDI MW = 168.2	0	87.2	3.5	0.02–946.7	0	305	81.3	10.1–1,714	3.0	0.9	0.1–16.8
HDI uretdione [d] MW = 336.4	45	727.6	1.7	< 0.1–10,288	59	457	0.02	0.02–7,354	5.3	< 0.1	< 0.1–60.8
HDI biuret MW = 478.7	20	855.2	18.4	< 0.1–8,240	23	3331	129.1	0.8–60,823	35.2	0.7	< 0.1–503.7
HDI isocyanurate MW = 504.7	25	27.2	3.4	< 0.1–182.3	27	236	24.2	1.0–2,303	4.4	0.1	< 0.1–39.2
Sum of species as total NCO (TNCO)	–	415.2	4.3	0.1–4,896	–	1049	134.6	12-16,558	11.2	0.7	0.1–137

[a] MW, Molecular weight (g/mol).
[b] Air sampling duration, which continued for the duration of the task, had a median of 105 min and range of 15–390 min.
[c] Glove sampling duration had a median of 117.5 min and range of 30–330 min.
[d] The higher percentage of non-detects for uretdione is due to this analyte's chemical instability owing to its unstable four-ring membered structure.



The enclosure variable was categorized in three main categories: tarp enclosures "Yes"; no enclosure, "no"; and indoor spraying, "indoor". Uretidinedione = uretdione.

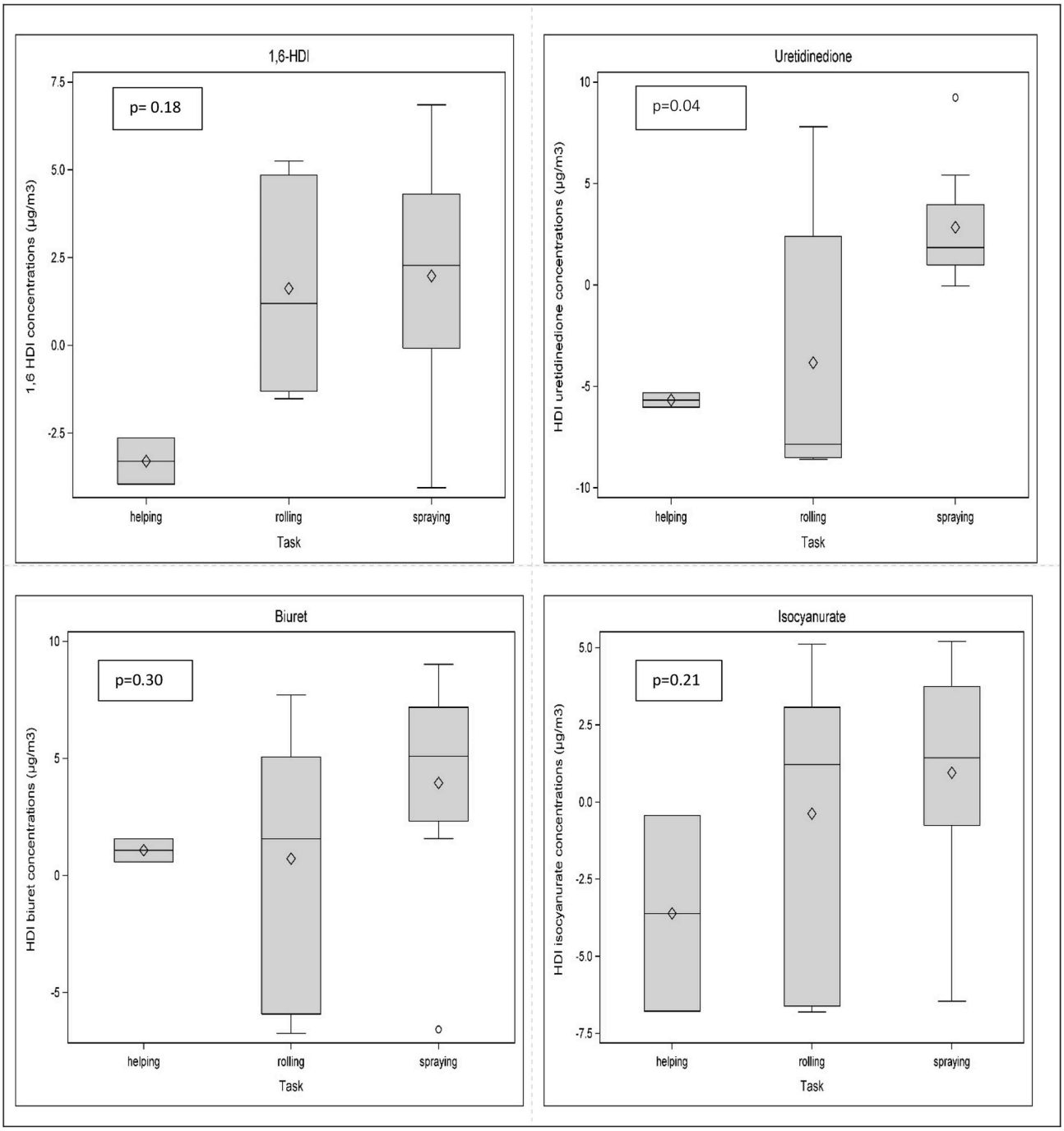
Fig. 3. Airborne ln-concentrations (µg/m^3) of HDI-based aliphatic isocyanate species by enclosure type[1]

3.4. Dermal exposures

The isocyanate load on gloves is summarized in Table 3. The highest loadings belonged to biuret (median, 129 µg/pair; range, 0.8–60,823), while the median for isocyanurate was 24.2 µg/pair of gloves (range, 1.0–2,303). The HDI monomer was detected in all samples, while oligomers were detected in 41–73% of samples. The lowest % of detectable samples was for uretdione, a finding similar to air samples (Table 3), and likely related to chemical instability of this analyte (based on stability experiments in the lab). The highest loading on the gloves was 60.8 mg biuret/pair and was measured during 121 min of indoor spray painting at the shop floor. Although spraying resulted in higher dermal exposures compared to rolling and helping, the results were not statistically significant (SI, Fig. S3).

3.5. Biomonitoring results

Descriptive statistics for urinary HDA normalized to creatinine and specific gravity (SG) are presented in Table 4, together with creatinine and specific gravity data. Urinary HDA was detected in all urine



Tasks performed were categorized in three main categories: 1) "spraying" when painting was done with a spray gun; 2) "rolling" when painting was done with a roller and/or a brush; 3) "helping" when product mixing and other supplementary tasks were performed. PBZ samples correspond to 8 spraying, 10 rolling, and 2 helping tasks. Uretidinedione = uretdione.

Fig. 4. Airborne ln-concentrations of HDI-based aliphatic isocyanate species (µg/m^3) by type of task performed.

samples, except for two pre-shift samples (96% detectable). The GM of HDA normalized to specific gravity (µg/L) in post-shift (GM 4.7, GSD 2.7) was significantly higher ($p < 0.001$) than the pre-shift samples (GM 1.9; GSD 4.8) and the ratio of post-shift/pre-shift GM ratio was 2.47. When the HDA data were normalized to creatinine, the post-shift/pre-shift GM ratio was 1.44, but the difference was no longer statistically significant ($p = 0.32$). Urinary specific gravity increased post-shift from (GM 1.02 to 1.03, $p = 0.026$) and so did creatinine (GM 19.1–34.4 mmol/L, $p < 0.001$).

The UK Health and Safety Executive has established a Biological Monitoring Guidance Value (BMGV) for isocyanates such as HDI and MDI, set at 1 µmol/mol creatinine (Jones et al., 2017). Among all urine samples collected, 58.6% exceeded the BMGV. The number of urine samples exceeding BMGV increased from 54% in pre-shift urine to 59% in post-shift samples, in spite of major increases in post-shift creatinine concentrations. Furthermore, workers who wore polyethylene coveralls had lower ($p = 0.03$ and 0.15 for SG and creatinine normalization, respectively) urinary HDA levels than workers who wore standard

Table 4
Cross-shift changes in the urinary biomarker hexamethylene diamine (HDA) normalized to creatinine and specific gravity.

Urinary biomarker	Pre-shift (n = 26)		Post-shift (n = 27)		Paired t -test on cross-shift differences
	GM (GSD)	Range	GM (GSD)	Range	p-value
HDA normalized to creatinine (μmol HDA/mol creatinine)	0.9 (5.7)	nd[a]-19.3	1.3 (2.3)	0.2–4.5	0.32
HDA normalized to specific gravity (μg/L)	1.9 (4.8)	nd-15.6	4.7 (2.7)	0.3–14.7	< 0.001
Creatinine (mmol/L)	19.1 (2.5)	1.3–53.9	34.4 (1.6)	11.4–86.0	< 0.001
Specific gravity	1.02 (1.0)	1.01–1.04	1.03 (1.0)	1.01–1.04	0.03

Pre- and post -shift urine samples were obtained for 21 painters, 4 helpers and 2 bystanders. One unpaired urine sample was collected post-shift from a bystander. Urinary HDA was detectable in all but two pre-shift samples that belonged to two helpers (one mixer at the wind turbine site and one at the reactor dome site who applied isocyanates with a roller and brush).
[a] nd, non-detectable.

clothing and cotton coveralls (SI, Fig. S4). Workers wearing half-facepiece cartridge respirators had lower urinary HDA compared to workers who did not use any respirator, although the results were not statistically significant (p = 0.80 and 0.45, for SG and creatinine normalization, respectively) (SI, Fig. S5). The type of glove in use was not associated with HDA levels (data omitted).

Univariate and multivariate models of post-shift HDA normalized to creatinine or specific gravity with air and dermal exposures as independent variables were restricted to the 16 samples collected among painters who provided matched air, glove and urine samples. In univariate analysis, as well as multivariate sub-models, the PBZ airborne HDI monomer exposures were a significant predictor of urinary HDA normalized to specific gravity, but not to creatinine (Table S6). Furthermore, neither dermal exposure to 1,6-HDI nor specific gravity were significant predictors of post-shift HDA levels in all multivariate sub-models with creatinine or/and specific gravity as independent variables. On the contrary, creatinine was a significant predictor of urinary HDA in multivariate modeling (p < 0.01–0.10) (Table 5). Similar results were obtained in univariate and multivariate models with air and dermal exposures to TNCO instead of HDI (data omitted). This may be due, in part, to strong correlation between HDI and other species (uretdione, biuret, isocyanurate and TNCO, SI Table S4).

4. Discussion

Isocyanate-based formulations such as coating products are used widely in numerous construction trades. Although common, exposures to aliphatic isocyanates during coating applications in construction have not been characterized. In this work, we report our findings of a field study to assess inhalation and dermal exposures to isocyanates, their work practices, and the current status of exposure controls, among 30 painters from ten sites in the Northeastern USA performing metal structure coating in construction. Urinary biomonitoring of HDA, one signature biomarker of aliphatic HDI-based isocyanates, in pre- and post -work shift urine samples and associations with inhalation and dermal exposures were also assessed. These findings, discussed in depth in subsequent sections, collectively indicate high potential for dermal and inhalation exposures, high body burden of HDI, inadequate exposure controls, and ample opportunities for intervention research to reduce such isocyanate exposures and associated health risks, including asthma and contact dermatitis.

4.1. Inhalation exposures and implications

Our results reveal exposure to high airborne concentrations of aliphatic isocyanates among construction painters in bridges and other metal structures. When compared to the existing occupational exposure standards or guidelines for isocyanates (Table 6), 20% of samples exceeded the NIOSH REL 10 min ceiling standard for 1,6-HDI (140 μg/m^3) and 35% of samples exceeded the UK-HSE 10-min ceiling standard for TNCO (70 μg/m^3). In addition, about 15–35% of samples exceeded the daily time weighted average (TWA) exposure limits for 1,6-HDI and TNCO, depending on the calculation assumption. Although high, these exposure concentrations appear to be lower than those measured in autobody shops in earlier work. For example, the SPRAY study (Sparer et al., 2004) reported > 92% of clear coating samples exceeded the HSE ceiling TNCO standards of 70 μg/m^3.

The chemistry of topcoat aliphatic isocyanates used in construction metal structure painting, as documented in this investigation, appears to be less variable than that in the auto refinishing industry. In this study we found in use only HDI-based prepolymers, and no pIPDI. In contrast, pIPDI was found blended with an HDI-based isocyanurate

Table 5
Summary of the multivariate models with creatinine and specific gravity as independent variables in 16 matched air, glove, and urine samples.

Models with creatinine					Models with specific gravity (SG)					Models with both creatinine and specific gravity				
Variable[1]	Parameter estimates	Pr. > t	95% Confidence limits		Variable	Parameter estimates	Pr. > t	95% Confidence limits		Variable	Parameter estimates	Pr. > t	95% Confidence limits	
PBZ	0.10	0.26	−0.1	0.2	PBZ	0.21	0.03	0.1	0.4	PBZ	0.1	0.23	−0.1	0.2
Creatinine	1.17	**0.04**	0.1	2.3	**SG**	−20.8	0.59	- 103	61	**Creatinine**	1.5	**0.02**	0.5	2.8
										SG	−50	0.17	−127	30
Gloves	< 0.01	0.99	−0.3	0.3	**Gloves**	−0.2	0.19	−0.5	0.1	**Gloves**	< 0.1	0.99	−0.3	0.3
Creatinine	1.62	< **0.01**	0.5	2.8	**SG**	1.4	0.96	−56	59	**Creatinine**	1.8	< **0.01**	0.5	3.1
										SG	−21	0.41	−74	32
PBZ	0.1	0.26	−0.1	0.3	**PBZ**	0.11	**0.05**	−0.7	4.4	**PBZ**	0.1	0.19	−0.1	0.3
Gloves	−0.01	0.92	−0.4	0.4	**Gloves**	−0.18	0.17	−0.6	0.2	**Gloves**	−0.1	0.66	−0.4	0.3
Creatinine	1.24	**0.10**	−0.3	2.8	**SG**	−24.5	0.32	−123	74	**Creatinine**	1.4	**0.06**	−0.1	3.0
										SG	−57	0.16	−141	26

Legend: The depended variable is the non-normalized Ln-post-shift urinary HDA. The independent variables consist of PBZ (Ln-HDI monomer personal breathing zone exposures in μg/m^3); Gloves (Ln-HDI monomer glove loading in μg/pair/min); Creatinine (ln-creatinine in mmol/L); and SG (ln-specific gravity, unitless).

Table 6
Personal breathing zone (PBZ) sampling results (n = 20) in comparison to the existing occupational exposure limits (OEL), without correcting for respirator use.

	HDI			TNCO (pHDI)	
	NIOSH REL		ACGIH	UK HSE	
	TWA 10hr	Ceiling[a] 10 min	TWA 8hr	TWA 8hr	Ceiling 10 min
OEL value (μg/m^3)	**35**	**140**	**34**	**20**	**70**
% of samples above OEL assuming same exposure for unsampled time (= whole shift)	25	20	25	35	35
% of samples above OEL assuming zero exposure for unsampled time [b]	15	na	20	25	na

TNCO, total NCO group summed across all quantified pHDI species. This approach underestimates true TNCO, as several other species are not measured and accounted for; na, not applicable.

[a] Comparison with the 10-min Ceiling value was based on the conservative assumption that exposure intensity remained constant for the whole sampling duration (range 30–330 min). Because of exposure variability, it is possible that some 10-min exposure intervals over the sampled time would exceed the average levels for the sampling duration, even when the average concentration is below the ceiling. As a result, the percentage of samples exceeding ceiling would be higher than currently estimated.

[b] Sampling duration equaled the whole painting/coating duration for the majority of samples.

product in 26% of the products in auto body shops (Sparer et al., 2004). In construction top coating applications, the main HDI oligomer was HDI biuret, whereas in body shops HDI isocyanurate and its blends with biuret and pIPDI (Fent et al., 2008; Sparer et al., 2004) were predominant in the product. However, far more complex chemistries were documented at intermediate coating Corothane formulations (Table 2). Compared to airborne concentrations measured in the breathing zone of automotive painters in (Fent et al., 2008), the median biuret concentration in our study was 4 × higher, whereas median isocyanurate levels were ~700 times lower. Similarly, the median HDI and uretdione in the current study were respectively 2.1 and 3 times lower than those reported in (Fent et al., 2008). In a study of shipyard industrial spray painters (Pronk et al., 2006), reports median oligomer concentrations of 199.9 μg/m^3 TNCO or 46.3 times higher than median TNCO of 4.3 μg/m^3 in the current study. Similarly, the same study by (Pronk et al., 2006) reports median TNCO concentration for top coats in the autobody refinishing industry of 116.3 μg/m^3 TNCO, or 27 times higher than in our study. Two main possible explanations for the overall lower isocyanate exposures in construction trades, are spraying outdoors and the more frequent application of roller and brush painting. However, it should be emphasized that inside enclosures on bridges we measured higher airborne isocyanate exposures (up to 4.9 mg TNCO/m^3 in this study, Table 3) than in shipyard industrial painting (2.6 mg/m^3) (Pronk et al., 2006) and in the same range with previous reports in autobody shops (Woskie et al. .2004) (Fent et al., 2008). High airborne isocyanate exposures are a major concern inside enclosures in bridges and other structures, in which heat, physical activity, and smells create ample opportunity for non-compliance with the PPEs.

The majority of painters (61%) in our study used half-facepiece vapor cartridge respirators with a nominal protection factor of 10. These respirators would provide acceptable protection against isocyanates in several exposure situations, such as short-term high peak exposures, and lower exposure scenarios (roller/brush painting, mixing, far field, etc.). However, they would be inadequate during high exposure scenarios. For example, in the case of bridge painters with TNCO exposures of 4,896 μg/m^3, the use of half face respirator would reduce exposures to 490 μg/m^3, a value that it is at least 3 × higher than the UK HSE ceiling limit of 140 μg/m^3. For HDI exposure levels > 0.125 ppm and up to 0.25 ppm, NIOSH recommends wearing respirators with an assigned protection factor (APF) of 50, which could be any self-contained breathing apparatus with a full facepiece or (b) any supplied-air respirator (SAR) with a full facepiece. In 10% of air samples (2/20), airborne HDI concentrations were higher than > 0.125 ppm, a scenario which, according to NIOSH recommendations, would require the use of any supplied air respirator operated in a continuous flow mode. Our field observations, high levels of urinary HDA biomarker data, and significant association with airborne HDI exposures, support the overall conclusion that respiratory protection is inadequate during spray painting of bridges and other enclosed metal structures.

4.2. Dermal exposures and implications

High isocyanate loading was measured on the glove dosimeters, at times as high as 1.7 mg HDI, 60.8 mg biuret, and 16.6 mg TNCO. Such high isocyanate loadings on gloves are a result of multiple contaminant transfer and deposition mechanisms, including contact with raw material, contaminated surfaces and tools, deposition of overspray aerosol, or direct spraying on hands, all observed to occur in the field. Direct skin contact with the paint was observed frequently for several body parts, especially forearms, hands, and face/head, which was more noticeable when workers wore short sleeve shirts (Fig. 2b). Dermal exposures to TNCO in this study are in the same range with those reported in (Pronk et al., 2006) for industrial painters (median TNCO in this study, 135 μg vs. up to 63 μg, or 2x higher). The sampling and analytical methods employed for dermal exposure in these two studies were similar (interception techniques and LC-ESI-MS/MS analysis) and results more directly comparable. However, the loading for the more volatile HDI monomer in our study was higher (median of 81 vs 0.5 μg) than in (Pronk et al., 2006) study, which is likely related to stabilization of HDI as a MAP derivative on the glove dosimeter. A reagent-impregnated glove dosimeter/sampler is advantageous to and preferred over a reagentless glove as it results in better collection efficiency for all isocyanate species. However, the differences in results between reagent-treated and reagentless samplers do not appear to be as large as for aromatic isocyanates (Harari et al., 2016), a finding that is attributed to the relatively lower reactivity of aliphatic isocyanates. In our earlier studies in autobody shops, we used skin wipes (a removal technique) to assess dermal exposure on bare skin (such as forearms and neck (Bello et al., 2008; Liu et al., 2007). The isocyanate skin surface density in these earlier studies was in the order of 1–100 ng/cm^2 TNCO, whereas TNCO loadings were < 10 μg/sample. When normalizing to the surface area sampled, the dermal exposure (potential) in this study was much higher than in our earlier studies in body shops, with the majority of point comparisons differing by 100–1000 × . It is likely that, in addition to real differences in exposures between bridge painting and body shops, the use of a more efficient interception dosimeter, combined with a much more sensitive analytical technique, may have played a role in our findings of much higher dermal exposures in metal structure coating.

(Fent et al., 2008) found that the use of gloves and coveralls during spray painting was significantly associated with a reduction on the total dermal exposures among automotive painters. One of the highest dermal exposures in our study was measured during painting at the indoor site and reflects proximity of hands to the sprayed parts, increasing the chance of overspray aerosol transferred to hands (Fig. 1, c). Given that 46% of participants used standard clothing with short sleeve shirts, and 14% didn't use any gloves during painting, dermal exposures among this group of workers should be prioritized for exposure reduction interventions.

In this study we measured the potential for dermal exposure to hands, the anatomical site with one of the highest potential for dermal exposure, as observed in our earlier studies in autobody shops (Bello et al., 2008; Liu et al., 2007). Similar findings were obtained from a

whole-body assessment of isocyanate distribution during spray foam application (SPF), which revealed that hands had the second highest dermal isocyanate loading, after the head and neck region (unpublished data). The isocyanate exposures to bare skin sites, such as hands, forearms, and neck and face, are a serious concern if one considers growing experimental and observational evidence that skin exposure is an effective pathway for inducing systemic sensitization (Bello et al., 2007; Cochrane et al., 2015; Redlich, 2010) and that single skin exposure episodes may suffice to induce dermal sensitization and elicit an allergic response on the skin (Geier et al., 2018). There are no statistics on the prevalence of contact dermatitis and other skin disorders in this cohort of workers.

4.3. Biomonitoring

The majority of the urine samples collected in our study (58.4%) had HDA values higher than the UK HSE biomonitoring guideline, indicating occupational exposures and inadequate protection, conclusions that are further reinforced by the significant cross-shift increases in HDA concentration. This perhaps should be expected given that approximately in 1/3 of cases, workers did not wear any respirators (32%), no gloves of any kind (14%), and no or inadequate coveralls in nearly half of the cases (46%). Overall, the percentage of urinary samples exceeding the BMGV of 1 μmol HDA/mol creatinine in this study (> 50%) are much higher than those reported in earlier studies 6% in (Jones et al., 2013); 0.5% in (Hu et al., 2017). No IPDA was found in any of the urine samples, which is consistent with lack of pIPDI in top coating products used at investigated study sites.

We found high potential for dermal exposures to pHDI, although isocyanate loading on gloves/hands was not significantly associated with urinary HDA. Such a finding may have alternative explanations, including insufficient sample size, much slower dermal absorption kinetics through the skin, such that the contribution of dermal exposure would not be observed at the end of the shift but rather next day(s), or skin absorption at anatomical sites other than hands (forehead, forearms, etc.). The high frequency of pre-shift urinary HDA exceeding the BMGV value (54%) likely reflects previous day/s dermal exposures, as well as prior systemic exposures. The half-life of HDA clearance through inhalation exposure is short, with an estimated half-life of ~3 h (Gaines et al., 2010a; Liu et al., 2004). The exact half-life of HDA clearance through dermal exposure is not known, but it is expected to be much slower. In experimental animals, dermal exposure to isocyanates would show in urine as isocyanate conjugates detected through isocyanate specific antibodies after 24 h (Wisnewski, personal communication). Direct evidence in support of this hypothesis in humans is limited (Jones et al., 2017). found positive association between MDI skin exposure and next day urine biomonitoring, but not same day post-shift urine. In this study we found that workers wearing polypropylene/polyethylene (PP/PE) coveralls had significantly lower levels of urinary HDA compared to those wearing standard clothing and cotton coveralls, which agrees with earlier reports (Fent et al., 2008). We have shown recently in permeation panel testing using realistic paint formulations and spray application techniques, that Tyvek® and PP/PE coveralls provided excellent protection against pHDI topcoats and midcoats, whereas cotton shirts provided only partial protection (Mellette et al., 2018). In that same study, we found that the thin nitrile gloves provided excellent protection against pHDI top coats, whereas latex gloves did not, a finding consistent with earlier investigations in the auto refining industry (Ceballos et al., 2014). A limitation of our study was the relatively small sample size that may have contributed to the lack of significant associations with some important exposure determinants and prevented us for conducting additional statistical analysis and imputations techniques.

In our study, HDA was detected in 98% of the urine samples collected, which is much higher than in other previous studies: 0.5% of the (n = 191) urine samples in a recent study of autobody shop workers in Australia (Hu et al., 2017); 8% of (n = 52) samples collected among industrial painters in the Netherlands (Pronk et al., 2006); 17% of (n = 995) urine samples in paint sprayers and managers in the automotive repair industry in the UK (Jones et al., 2013); 30% (n = 70) of urine samples of workers in wide a range of polyurethane industry sectors (Creely et al., 2006); to 62% (n = 427) of urine samples in automotive workers (Gaines et al., 2010a). Considering our earlier comparative analysis of exposure levels and work practices across these studies, it appears that the much higher sensitivity in our study is likely primarily due to notable improvements in the absolute HDA recovery (~5 -15 ×) with the modified sample preparation step (SI, Table S3), and partly due to higher exposures and poor hygiene practices.

Urinary HDA concentrations in our study were generally much higher than in earlier studies in body shops workers, and comparable to the highest HDA biomonitoring values reported in the literature. For example, a study of sprayers in automobile repair shops (Gaines et al., 2010a) reported an overall GM of HDA of 0.1 μg/L compared to 1.4 μg/L (in all of our urine samples) (Jones et al., 2013). reported a median HDA value of 0.10 μmol/mol creatinine, which is 10 × lower than in this study. The 90th percentile of 0.6 μmol/mol creatinine in Jones et al. (2013), is much lower than in this study (4 μmol/mol creatinine), whereas the maximums are comparable (21 vs 19.3 μmol/mol creatinine, respectively). In addition (Creely et al., 2006), reports GM HDA levels of 0.29 μmol/mol creatinine in urine samples of workers in wide a range polyurethane industry sectors, which are 3 × lower than in this study (GM of 1.4 μmol/mol creatinine for all samples). In a chamber study of human volunteers exposed to pHDI (Liu et al., 2004), reported mean urinary HDA immediately post-exposure (highest values observed) of 18.1 μg/g creatinine (17.6 μmol/mol), which dropped rapidly to 3.2, 1.3, and 0.74 μmol/mol creatinine at 4, 9 and 17 h post-exposure, respectively. These later HDA urinary clearance values are in the same range with the values found in our study.

Urinary biomonitoring is a desirable non-invasive technique in occupational and environmental health research. One challenge with urinary biomonitoring relates to changes in the urinary dilution rates as a result of hydration status and sweating. This problem is addressed typically using creatinine adjustment and specific gravity adjustments by dividing the biomarker concentrations by the creatinine/specific gravity concentrations. Creatinine normalization is used more frequently in the field of occupational health and for this reason most guidance values for isocyanates and other exposure biomarkers are based on creatinine normalization. Creatinine is cleared from the body through the kidney by glomerular filtration. Urinary creatinine may increase as a result of heat stress, workload/muscle degradation, and kidney toxicity (Barr et al., 2005). found that creatinine excretion in the morning was significantly lower than evening. In this cohort of workers we found highly and statistically significant cross-shift changes in creatinine levels ($p < 0.001$): 48% of pre-shift and 80% of post-shift urine samples had creatinine concentrations above the World Health Organization (WHO) upper normal guidance value of 300 mg/dL for workplace biomonitoring (World Health Organization, 1996). Such highly unusual and repeatable observations suggest that creatinine in this cohort could be excreted at a non-constant rate during the workday, an outcome driven by heat stress and dehydration experienced by workers during painting, high physical activity, mixed chemical exposures to isocyanates and other part B ingredients (including solvents). Cross-shift increases in urinary creatinine have been reported in earlier cohorts of workers in auto body shops (Gaines et al., 2010b), and in our cohort of SPF workers (Bello et al., 2019). However, the phenomenon is much more profound in this study of construction bridge and steel structure painters than in auto body shop workers (Gaines et al., 2010b) or SPF workers (Bello et al., 2019). No cross-shift or cross-week changes in creatinine levels have been observed in administrative office workers and photocopier operators who work indoors, have ample opportunities to stay hydrated and experience a much lower physical workload (Khatri et al., 2017). Potential

nephrotoxicity in this cohort of workers, suggested by additional urinary biomarkers of kidney toxicity, deserves more in-depth follow-up investigations.

Our data suggest that normalization of HDA to creatinine could lead to substantial bias towards the null when investigating cross-shift biomarker changes in this cohort of workers. For example, the post-shift mean urinary HDA was statistically significantly higher than the pre-shift mean HDA, when normalized to SG (paired *t*-test on ln-transformed data, $p < 0.001$, Table 4), but not when normalized to creatinine ($p = 0.32$). Modeling results were also impacted by the normalization approach. Airborne PBZ exposures were a statistically significant predictor of urinary HDA in models with HDA normalized to SG, but not in models with HDA normalized to creatinine. Similarly, airborne PBZ exposures were a significant predictor of urinary HDA only in the models containing SG as an independent variable. Furthermore, correlation between SG and creatinine in urine was stronger in pre-shift samples than post-shift samples (correlation coefficient 0.72 vs. 0.35, respectively). These findings collectively suggest that normalization to SG may be more suitable for biomonitoring of urinary HDA among construction painters than the traditional creatinine normalization.

This discussion would not be complete without a discussion of the limitations of the HDA biomarker. HDA is the only established biomarker for aliphatic pHDI isocyanates. HDI is a minor constituent of the total pHDI species. Because of its higher volatility and lower molecular weight, biokinetics of HDI clearance may be different from those of higher pHDI species. Distribution and clearance biokinetics of higher HDI oligomers are not known. Whether these higher oligomers contribute to HDA in urine is not known, but it is unlikely. For all these reasons, HDI biomonitoring via HDA should be interpreted with caution. On the other hand, airborne HDI concentrations in spray applications correlate well with biuret (R^2, 0.85, isocyanurate (R^2, 0.82) and uretdione (R^2, 0.95), as well as with TNCO (R^2, 0.8), and HDA may serve as a surrogate biomarker of total isocyanate exposures. A new biomarker for HDI isocyanurate, namely the corresponding triamine obtained by similar acid hydrolysis has been reported recently (Robbins et al., 2018). The utility of this biomarker for routine biomonitoring purposes of aliphatic isocyanates rich in isocyanurate has to be evaluated further. Given the variability in product formulations across different applications, and that airborne biuret and isocyanurate are only moderately correlated (R^2, 0.54 in this study), simultaneous biomonitoring of higher oligomers of biuret and isocyanurate is highly desirable.

5. Conclusions

Exposure and biomonitoring results, in conjunction with field observations, support the overall conclusions that (a) substantial exposures to isocyanates occur during industrial coating applications among construction painters; and that (b) the current exposure controls are not sufficiently protective. Implementation of effective exposure control programs focusing on tasks performed in enclosed spaces and increased awareness about proper PPE use are warranted in order to reduce isocyanate inhalation and dermal exposures among these construction workers. In future work, we intend to develop specific interventions strategies and evaluate their effectiveness in the field.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijheh.2020.113495.

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